PC Codes 128967
EPA REG No. 7173-ELI

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

27/JUL/2007

MEMORANDUM

Subject: Name of Pesticide Product: Difethialone Paste Place Packs
EPA Reg. No. /File Symbol: 7173-ELI
DP Barcode: 338437
Decision No: 374677
PC Code: 128967 Difethialone

From: Tracy Keigwin
Technical Review Branch
Registration Division (7505C)

Byron T. Backus 7-27-2007

To: Daniel Peacock, RM 07
Insecticide-Rodenticide Branch
Registration Division (7505C)

Applicant: Liphatech, Inc.
3600 W. Elm Street
Milwaukee, WI 53209

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Difethialone	0.0025
Inert Ingredient(s):	99.9975
Total:	100.0000%

ACTION REQUESTED: PM requests review of acute toxicity data in support of Difethialone Paste Place Packs, EPA File Symbol 7173-ELI.

BACKGROUND: Liphatech, Inc. has submitted 5 acute toxicity studies (MRIDs 47052102-47052106) and one acute inhalation toxicity waiver in support of Difethialone Paste Place Packs, EPA File Symbol 7173-ELI. This is a paste-formulation rodenticide with residential, agricultural, commercial and industrial applications. The 5 submitted acute toxicity studies were conducted at Phycher Bio-Développement, 18, Chemin Lou Tribail, Zl de Toctoucau, F-33611 CESTAS Cedex, France.

OF NOTE: The test substance in the submitted studies is referred to as both "Difethialone Paste 0601" and "Difethialone Pate Bleue 25 mg/kg". The registrant has confirmed that these are alternate or internal names for the subject (e-mail correspondence from R. Callies to T. Keigwin, 7/23/2007).

OF ADDITIONAL NOTE: In the submitted acute inhalation toxicity waiver the registrant has stated that the product is "…a paste formulation, which is not friable and will not produce respirable particulates during normal handling and use…". We agree that it is unlikely one could inhale a paste and will accept an acute inhalation toxicity waiver for this product. Note that if the formulation or composition of this product changes this waiver must be re-evaluated in case the new formulation will be more readily inhaled.

OF FINAL NOTE: The acute dermal toxicity study (MRID 47052103) is unacceptable. EPA Guidelines state that a solid formulation should be moistened with diluent to ensure good contact with the skin; however this product is already a paste formulation. It was not diluted for the dermal irritation study, and was applied at 100% concentration for the dermal sensitization induction and some challenge applications. To dilute it as much as was used for the acute oral study was excessive and could have reduced the potential acute dermal toxicity of this product.

Likewise, the dermal sensitization study (MRID 47052106) is also unacceptable. The study provides the dates of 3 positive control studies, however the one that utilized the same test method as the main study (Buehler, 9 induction applications) was conducted 15 months prior to the date of the main study. Per Guideline requirements (OPPTS 870.2600), the method of validation must be the same as the method used on the test

substance and must be conducted within 6 months of the main study. MRID 47052106 may be upgradeable if the performing laboratory can cite a positive control study, using the Buehler method with 9 applications, which was conducted within 6 months of the main test study. Otherwise, a new dermal sensitization study must be submitted or cited.

RECOMMENDATIONS: We will accept the acute inhalation toxicity waiver with the conditions detailed above. The preliminary acute toxicity profile for EPA File Symbol 7173-ELI is as follows:

acute oral toxicity	III	Acceptable	MRID 47052102
acute dermal toxicity	-	**Unacceptable**	MRID 47052103
acute inhalation toxicity	waived		
primary eye irritation	IV	Acceptable	MRID 47052104
primary skin irritation	IV	Acceptable	MRID 47052105
dermal sensitization	No	**Unacceptable**	MRID 47052106

PRECAUTIONARY LANGUAGE. We will provide the product branch with the appropriate precautionary labeling for this product when the deficiencies, as detailed above, are resolved.

PC Codes 128967
EPA REG No. 7173-ELI

DATA EVALUATION RECORD

Reviewer: Tracy Keigwin July 27, 2007
Product Manager (EPA): 07

STUDY TYPE: Acute Oral Toxicity - Sprague-Dawley rat; OPPTS 870.1100; OECD 423

TEST MATERIAL (% a.i.): Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

CITATION: Richeux, F. Assessment of Acute Oral Toxicity in Rats, Acute Toxic Class Method. Facility Project Identification No.: TAO423-PH-06/0316. Phycher Bio-Développement, 18, Chemin Lou Tribail, ZI de Toctoucau, F-33611 CESTAS Cedex, France. September 20, 1996. MRID 47052102. Unpublished

SUBMITTER: Liphatech, Inc., 3600 W. Elm Street, Milwaukee, WI 53209

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47052102), 6 female Sprague-Dawley (SPF Caw) strain were given a single oral dose of Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste at a dose level of 2000 mg/kg. The test substance was diluted with distilled water and administered at a dose volume of 10 mL/kg. An additional 6 animals were treated with distilled water only (dose volume 2 mL/kg) to and served as a control group rats (source: Elevage Janvier, 53940 Le Genest St Isle - France; age: 8-9 weeks; weight: 197-206g). Animals were inspected for clinical abnormalities and mortality at 0.5, 1, 3 and 4 hours after dosing and additionally once daily for up to 14 days. Bodyweights were obtained on study days 0, 2, 7 and 14. A necropsy examination was performed on all test animals.

All animals (6/6 control; 6/6 test material) survived to study termination. No signs of toxicity were observed in either group. All animals gained weight throughout the study. No abnormalities were observed at necropsy.

The Oral LD_{50} in females is greater than 2000 mg/kg. EPA Toxicity Category III.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose Level (mg/kg)	Mortality/Number Tested Females
0	0/6
2000	0/6

A. Mortality - As listed above.

B. Clinical observations – All animals (6/6 control; 6/6 test material) survived to study termination. No signs of toxicity were observed in either group. All animals gained weight throughout the study. No abnormalities were observed at necropsy.

C. Gross Necropsy – No abnormalities were observed at necropsy.

D. Reviewers Conclusions: Agree with study author that the acute LD_{50} for this product is greater than 2000 mg/kg.

E. Deficiencies – None.

PC Codes 128967
EPA REG No. 7173-ELI

DATA EVALUATION RECORD

Reviewer: Tracy Keigwin July 27, 2007
Product Manager (EPA): 07

STUDY TYPE: Acute Dermal Toxicity - Sprague Dawley Rats; OPPTS 870.1200; OECD 402

TEST MATERIAL (% a.i.): Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

CITATION: Richeux, F. Assessment of Acute Dermal Toxicity in Rats, Acute Toxic Class Method. Facility Project Identification No.: TAD-PH-06/0316. Phycher Bio-Développement, 18, Chemin Lou Tribail, ZI de Toctoucau, F-33611 CESTAS Cedex, France. September 20, 1996. MRID 47052103. Unpublished

SUBMITTER: Liphatech, Inc., 3600 W. Elm Street, Milwaukee, WI 53209

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47052103), 5 male and 5 female Sprague-Dawley (SPF Caw) strain rats (source: Elevage Janvier, 53940 Le Genest St Isle - France; age: males 7 weeks, females 8 weeks; weight: males 258g – 267g, females 212g-223g) were dermally exposed to Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste at a dose level of 2000 mg/kg (diluted with distilled water, dose volume 10 mL/kg). An additional 5 male and 5 female animals were treated with distilled water only (dose volume 2 mL/kg) and served as a control group. The test substance (diluted with distilled water, dose volume 10 ml/kg) was administered to test animals and covered with a porous gauze dressing. Control animals received an administration of 2 mL/kg of distilled water, which was covered with the gauze dressing. The study does not state how long the dressings remained on test and control animals. Animals were inspected for clinical abnormalities and mortality at 1, 3 and 5 hours after dosing and additionally once daily for up to 14 days. Bodyweights were obtained on study days 0, 2, 7 and 14. A necropsy examination was performed on all test animals.

Dermal LD_{50} Males > 2000 mg/kg bw (0/5 died)
Dermal LD_{50} Females > 2000 mg/kg bw (0/5 died)
Dermal LD_{50} Combined > 2000 mg/kg bw (0/10 died)

All animals (5/5 males, 5/5 females) survived to study termination. No signs of systemic toxicity were observed. The test substance did not affect bodyweight gain. There were no signs of dermal irritation.

No abnormalities were observed at necropsy.

Toxicity based on the lack of mortality observed in both the male and female rat. EPA Toxicity Category III.

This acute dermal study is classified as unacceptable. EPA Guidelines state that a solid formulation should be moistened with diluent to ensure good contact with the skin; however this product is already a paste formulation. It was not diluted for the dermal irritation study, and was applied at 100% concentration for the dermal sensitization induction and some challenge applications. To dilute it as much as was used for the acute oral study was excessive and could have reduced the potential acute dermal toxicity of this product.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
2000	0 / 5	0 / 5	0 / 10

A. Mortality - as noted in table.

B. Clinical observations - All animals (5/5 males, 5/5 females) survived to study termination. No signs of systemic toxicity were observed. The test substance did not affect bodyweight gain. There were no signs of dermal irritation.

C. Gross Necropsy – No gross abnormalities were observed at necropsy.

D. Reviewers Conclusions: Although the study suggest the test material is in Category III in terms of dermal toxicity, the test material was excessively diluted.

E. Deficiencies – Detailed above

Reviewer: Tracy Keigwin July 27, 2007
Product Manager (EPA): 07

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL (% a.i.): Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

CITATION: Richeux, F. Assessment of Acute Eye Irritation. Facility Project Identification No.: IO-OCDE-PH-06/0316. Phycher Bio-Développement, 18, Chemin Lou Tribail, ZI de Toctoucau, F-33611 CESTAS Cedex, France. September 20, 1996. MRID 47052104. Unpublished

SUBMITTER: Liphatech, Inc., 3600 W. Elm Street, Milwaukee, WI 53209

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47052104), 0.1 ml of Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste was instilled into the right eye of 3 male New Zealand White rabbits [source: Elevage de Gérome (Quartier Labaste – F40260 Linxe); age: not provided; weight: 2.18 kg – 2.50 kg]. Animals were observed for ocular irritation at 1, 24, 48, and 72 hours post instillation.

No corneal opacity, iritis or positive signs of conjunctivitis were observed in any of the test animals during the study. EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

	Number "positive"/number tested			
	Hours			
Observations	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae[a]:				
Redness	0/3	0/3	0/3	0/3
Chemosis	0/3	0/3	0/3	0/3
Discharge	0/3	0/3	0/3	0/3

[a] Score of 2 or more required to be considered a positive.

A. Observations No corneal opacity, iritis or positive signs of conjunctivitis were observed in any of the test animals during the study. Please note that the study does record signs of conjunctivitis, however the scores (grade 1) are not considered positive per 870.2400.

B. Reviewers Conclusions: TRB agrees with the results reported by the study author (as listed above), placing this product in Toxicity Category IV for primary eye irritation.

C. Deficiencies - None

Reviewer: Tracy Keigwin July 27, 2007
Product Manager (EPA): 07

STUDY TYPE: Primary Dermal Irritation - New Zealand White rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL (% a.i.): Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

CITATION: Richeux, F. Assessment of Acute Dermal Irritation. Facility Project Identification No.: IC-OCDE-PH-06/0316. Phycher Bio-Développement, 18, Chemin Lou Tribail, ZI de Toctoucau, F-33611 CESTAS Cedex, France. September 20, 1996. MRID 47052105. Unpublished

SUBMITTER: Liphatech, Inc., 3600 W. Elm Street, Milwaukee, WI 53209

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47052105), 3 female New Zealand albino rabbits [source: Elevage de Gérome (Quartier Labaste – F40260 Linxe); age: not provided; weight: 2.35 kg – 2.59 kg]. were dermally exposed to Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste. An application of 0.5 mL of undiluted test substance was applied to an intact (undamaged) skin area on the right flank of each animal. The test substance was covered with a patch (the study does not specify what type) and secured with a strip of surgical gauze. Animals were observed for erythema and edema at 1, 24, 48, and 72 hours after patch removal.

Very slight (grade 1) erythema was observed in 1/3 test animals at the 1 and 24 hour observations, resolving by the 48 hour reading. No edema was observed at any time during the study. EPA Toxicity Category IV. PDI = 0.17.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

		Hours			
		1	24	48	72
A7595 Female	Erythema	1	1	0	0
	Edema	0	0	0	0
A7621 Female	Erythema	0	0	0	0
	Edema	0	0	0	0
A7622 Female	Erythema	0	0	0	0
	Edema	0	0	0	0

A. Observations – Very slight (grade 1) was observed in 1/3 test animals at the 1 hour observation, resolving within 48 hours. No edema was observed at any time during the study. EPA Toxicity Category IV.

B. Results - PDI – 0.17

C. Reviewers Conclusions – Product is category IV for primary dermal irritation.

D. Deficiencies – None

Reviewer: Tracy Keigwin July 27, 2007
Product Manager (EPA): 07

STUDY TYPE: Dermal Sensitization – Guinea Pigs; OPPTS 870.2600; OECD 406

TEST MATERIAL (% a.i.): Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

CITATION: Richeux, F. Assessment of Sensitising Properties on Albino Guinea Pig by Repeated Applications Buehler Test with 9 Applications. Facility Project Identification No.: SMB-9-PH-06/0316. Phycher Bio-Développement, 18, Chemin Lou Tribail, ZI de Toctoucau, F-33611 CESTAS Cedex, France. October 16, 1996. MRID 47052106. Unpublished

SPONSOR: Liphatech, Inc., 3600 W. Elm Street, Milwaukee, WI 53209

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47052106) with Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste, 30 [test group – 12 females, 8 males; naive control group (challenge) – 5 male and 5 females] Dunkin-Hartley strain guinea pigs (source: Centre de Production Animale (F-45160 Olivet; age: not provided; weight: males 370-522, females 361-468g at study initiation) were tested using the method of Buehler. Based on an initial screening with 4 subjects, it was determined that a 100% concentration of the test substance was appropriate for the induction application. An undiluted concentration and a 50% concentration in distilled water were selected for the challenge applications. For induction the test substance was applied three times a week for 3 weeks with 6-hour occluded exposure.

Following challenge, no positive responses (all scores were zero) were observed in test (19 animals) and naïve control (9 animals) at both the undiluted and 50% concentration test sites. One female in the induced group was found dead on day 9. This death was not attributed to exposure to the test material. One control female was found dead on day 35, the day of challenge (although no information is provided as to whether or not this animal was exposed to the test substance). Again, this death was not attributed to exposure to the test material.

The procedures were validated within 14 months of this study using undiluted HCA and 50% HCA at challenge.

In this study, the test substance is a dermal sensitizer.

This study is classified as **unacceptable**. The study provides the dates of 3 positive control studies; however the one that utilized the same test method as the main study (Buehler, 9 induction applications) was conducted 15 months prior to the date of the main study. Per Guideline requirements (OPPTS 870.2600), the method of validation must be the same as the method used on the test substance and must be conducted within 6 months of the main study. Additionally, the study does not state how much of the test substance was applied, nor if the application sites were clipped prior to application. MRID 47052106 may be upgradeable if the performing laboratory can cite a positive control study, using the Buehler method with 9 applications, which was conducted within 6 months of the main test study. Otherwise, a new dermal sensitization study must be submitted or cited.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction – At induction, test animals received a topical application of the test substance (amount not stated) three times a week for 3 weeks. Test sites were covered with occlusive dressing. "After each induction excess test substance was removed by a rinse with distilled water". No dermal readings were recorded after each induction application.

B. Challenge – Sixteen days following the last induction application the challenge was conducted with a 100% concentration of the test substance and a 50% concentration of the test substance in distilled water. The test areas were covered with occlusive dressing. The irritation response was noted at 24 and 48 hours after application.

D. Naive Controls (challenge) - Ten naive control guinea pigs were treated with a 100% concentration of the test substance and a 50% concentration of the test substance in distilled water. The test areas were covered with occlusive dressing. The irritation response was noted at 24 and 48 hours after application.

II. RESULTS and DISCUSSION:

Reactions and duration - Following challenge, no positive responses (scores all zero) were observed in test or naïve control animals at either the undiluted or 50% concentration test substance application sites.

B. Positive control – The results of the positive control were appropriate.

C. Reviewers Conclusions: While there was no indication that this formulation is a dermal sensitizer, the cited positive control study was not conducted within 6 months of this study.

D. Deficiencies – Detailed above.

ACUTE TOX ONE-LINERS

1. DP BARCODE: 338437
2. PC CODES: 128967
3. CURRENT DATE: 27/JUL/2007
4. TEST MATERIAL: Difethialone Pate Bleue 25 mg/kg; Batch Number F328; Purity 29.45 mg/kg; Blue Paste.

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Phycher Bio-Développement Lab Study # TAO423-PH-06/0316 Date: September 20, 1996	47052102	LD_{50} > 2000 mg/kg	III	A
Acute dermal toxicity/rat Phycher Bio-Développement Lab Study # TAO423-PH-06/0316 Date: September 20, 1996	47052103	LD_{50} > 2000 mg/kg	III	U
Primary eye irritation/rabbit Phycher Bio-Développement Lab Study # TAO423-PH-06/0316 Date: September 20, 1996	47052104	No corneal opacity, iritis, or positive signs of conjunctivitis observed	IV	A
Primary dermal irritation/rabbit Phycher Bio-Développement Lab Study # TAO423-PH-06/0316 Date: September 20, 1996	47052105	PDI = 0.17	III	A
Dermal sensitization/guinea pig Phycher Bio-Développement Lab Study # TAO423-PH-06/0316 Date: September 20, 1996	47052106	Not a sensitizer	NO	U

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived